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Cardiomyopathy in the fetus

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Introduction

Fetal cardiomyopathy is an infrequent occurrence and accounts for a small proportion of cardiac abnormalities observed during fetal life.[1] Cardiomyopathies are important because the reported mortality of affected fetuses is high and the cardiac findings may provide a clue to an underlying disease process. In this chapter, emphasis is placed on the echocardiographic features of fetal cardiomyopathies. There are relatively few data in the literature on the causes of cardiomyopathy during fetal life, but the causes reported to date will be given.

Classification

The classification of cardiomyopathies used in this chapter is the subdivision of cases into dilated cardiomyopathy and hypertrophic cardiomyopathy. A dilated cardiomyopathy is defined as a group of conditions where the left and/or right ventricle is dilated above the normal range with diminished systolic function. The term hypertrophic cardiomyopathy is used to describe fetuses in which the left and/or right ventricle is abnormally hypertrophied, without there being a structural cardiac abnormality sufficient to explain such hypertrophy. Cases with abnormal cardiac connections are not discussed.

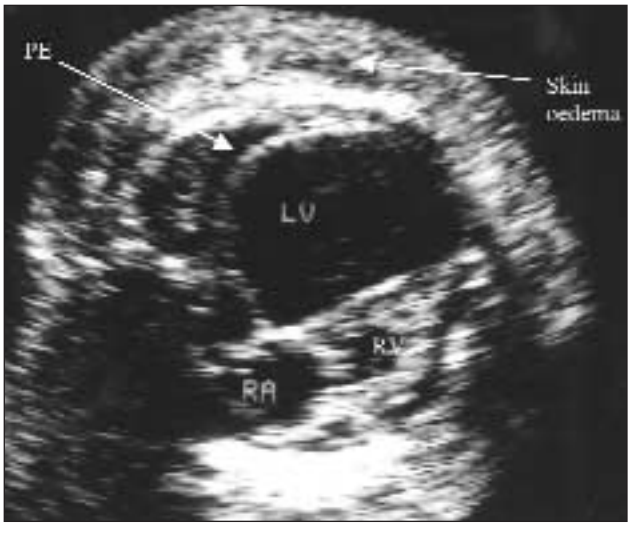
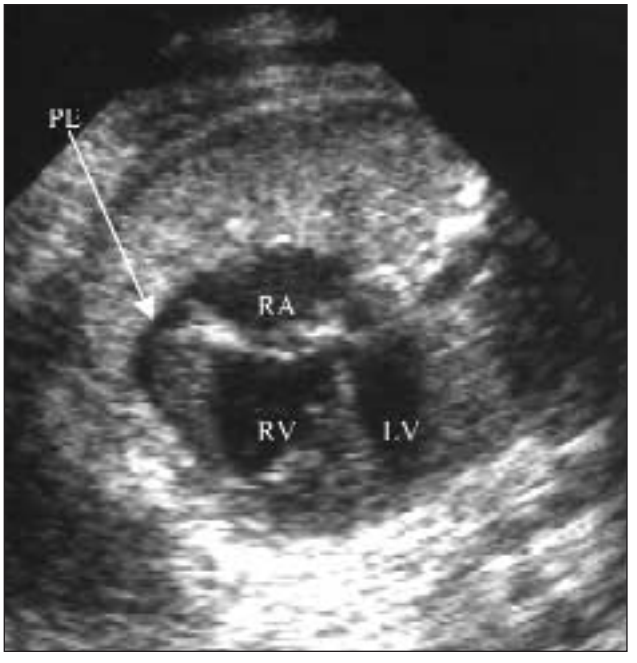


Figure 24.1
Dilated cardiomyopathy affecting the left ventricle (LV). The left ventricle is severely dilated and had minimal contraction. The right ventricle (RV) is relatively unaffected and contracted well. The heart virtually filled the chest and there was little lung tissue visible. There is skin oedema and a pericardial effusion (PE) posterior to the left ventricle. RA, right atrium.

Dilated cardiomyopathy

Echocardiographic features

The cardiothoracic ratio is invariably increased. Dilated cardiomyopathy can affect the left ventricle, the right ventricle, or both. Examples of affected fetuses are shown in Figures 24.1, 24.2 and 24.3. M-mode echocardiography confirms the reduced systolic function in such fetuses, which may be so severe that there is little or no contraction of the affected ventricle (Figure 24.4). Severe dilatation of the ventricles may lead to atrioventricular valve regurgitation (Figure 24.5). In some cases ventricular function is so poor that fetal hydrops results (Figure 24.6). As well as the reduction in systolic function, diastolic ventricular function is also abnormal. A case of dilated cardiomyopathy affecting the right ventricle is shown in Figures 24.2. In this case the mitral valve Doppler inflow pattern was normal but that of the tricuspid valve was



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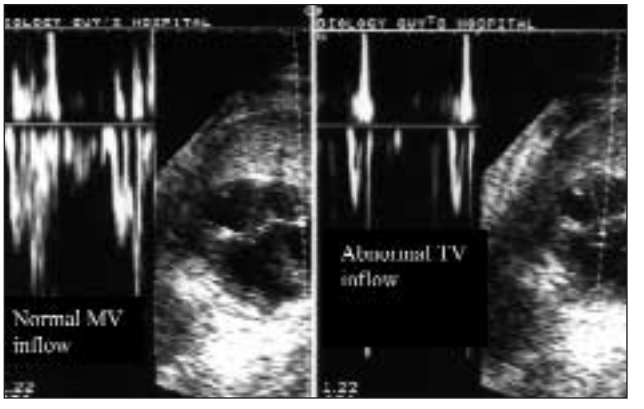

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Figure 24.2
(a) Fetal cardiomyopathy affecting the right ventricle (RV). The right ventricle is dilated and had minimal contraction. The right ventricle also appears mildly hypertrophied. The left ventricle (LV) was normal with goood systolic function. There is a pericardial effusion (PE) around the right ventricle. RA, right atrium. (b) Doppler inflow patterns of fetus with right ventricular cardiomyopathy shown in (a). There are normal e- and a-waves in the mitral inflow pattern of the unaffected left ventricle. Tricuspid valve (TV) inflow pattern is abnormal, with only a single inflow peak corresponding to the a-wave. MV, mitral valve.

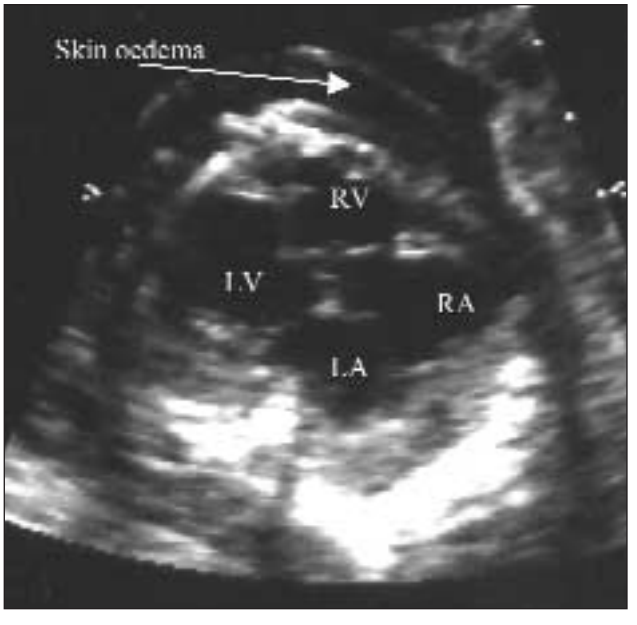


Figure 24.3
Fetal cardiomyopathy. In this example there is marked cardiomegaly, little lung tissue is visible and there is skin oedema. LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium.

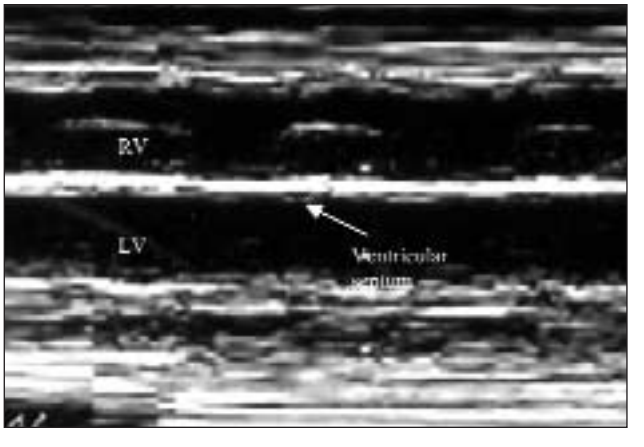


Figure 24.4
M-mode echocardiogram from a fetus with negligible contraction of either the right (RV) or left ventricle (LV).

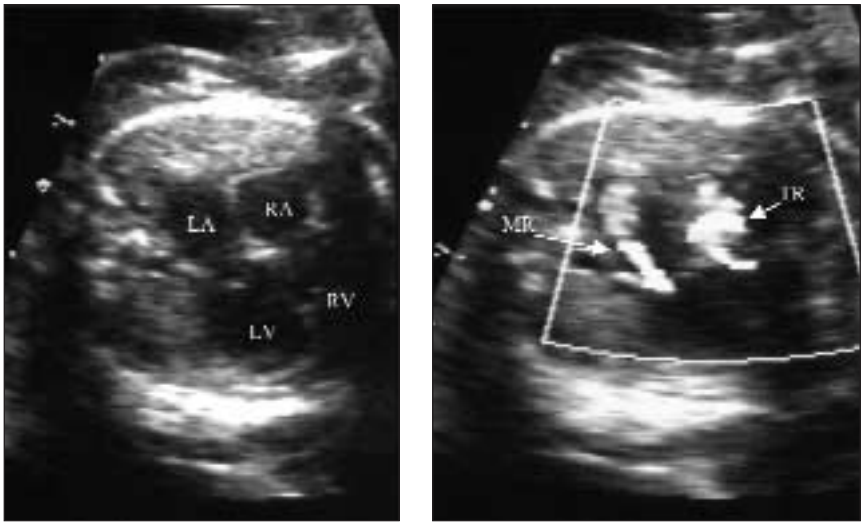


Figure 24.5
Atrioventricular valve regurgitation in a fetus with dilated cardiomyopathy. There is marked tricuspid and mitral regurgitation secondary to dilatation of the right (RV) and left ventricle (LV). LA, left atrium; RA, right atrium; MR, mitral regurgitation; TR, tricuspid regurgitation.

abnormal, with only a single inflow velocity peak corresponding to atrial contraction (a-wave).

Previous series

There is, to date, only one case series of dilated cardiomyopathy in the fetal literature.[2] That study reported six fetuses in which five had abnormal indices of systolic function. In three cases there was atrioventricular regurgitation secondary to ventricular dilatation. It is of note that, in two cases, the initial echocardiographic studies performed at 20 weeks of pregnancy were normal and the cardiomyopathy became evident only with advancing gestation. Death occurred in four of the six cases and one of the survivors required a heart transplant.

These data are very similar to our own experience at Guy's Hospital in London. Of 23 cases of dilated cardiomyopathy presenting between 1981 and 1998, the left ventricle was affected in six cases, the right ventricle in eight cases and both ventricles in nine cases. Ten fetuses were hydropic at presentation, and all of these died. Seven fetuses (30%) died in utero and eight (35%) died in the neonatal period. Overall, only four of the 23 fetuses survived.[3]

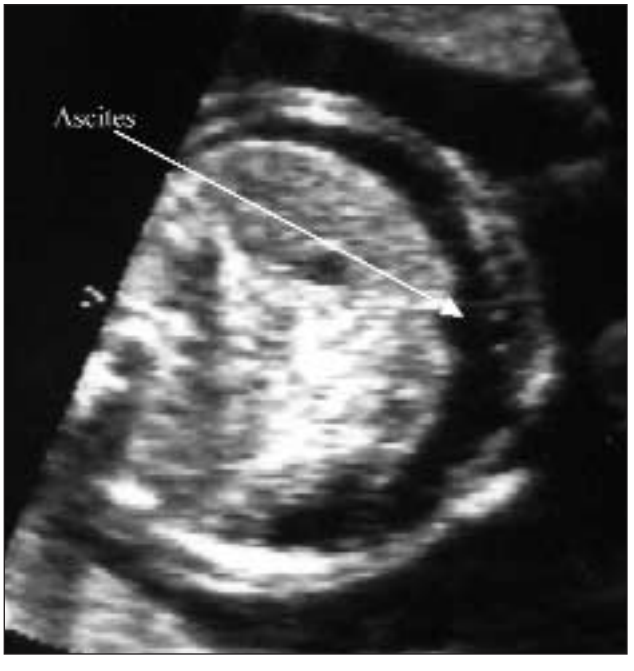


Figure 24.6
Ascites in a fetus with a dilated cardiomyopathy affecting both right and left ventricles.

Causes of dilated cardiomyopathy

Dilated cardiomyopathy may be the end result of a number of different disease processes. Table 24.1 lists the causes of dilated cardiomyopathy that have been reported in the literature. These include viral infections, metabolic disease and fetal anaemia. The cases of fetal anaemia probably represent the "end-stage" of very severe fetal anaemia. In both of these cases the haemoglobin level was less than 2 g/dl and one fetus survived following intrauterine transfusion. Other authors have published data confirming increased Doppler velocities and cardiac

Table 24.1. Causes of dilated cardiomyopathy reported in the fetus

Infective
Maternal HIV infection[11]
Coxsackie infection[11]
Toxoplasmosis[1]
Parvovirus[1]

Metabolic
Mitochondrial cytopathy[6,11]
Sialic acid storage disease[11]

Haematological
Fetal anaemia[11] (One of these cases was Blackfan–Diamond anaemia inherited from the mother)
Twin–twin transfusion syndrome

Arrhythmia
Post-tachycardia[6]

Idiopathic
Endocardial fibroelastosis[6]

output in anaemic fetuses prior to intrauterine transfusion.[4,5] Our cases probably represent a minority of fetuses with anaemia so severe that myocardial function is compromised. Therefore, fetal blood sampling should be considered to exclude fetal anaemia as a possible underlying cause of dilated cardiomyopathy.

Fetal cardiomyopathy may result from sustained fetal tachycardias. In such cases, the depressed cardiac function usually improves spontaneously following successful therapy for the underlying arrhythmia,[6] although complete resolution may take several weeks.

Investigation of dilated cardiomyopathy in the fetus

Following a diagnosis of dilated cardiomyopathy there should be a thorough investigation for possible underlying causes. Appropriate maternal samples should be taken for viral studies as well as a TORCH screen. Consideration should be given to fetal blood sampling to exclude anaemia, but this procedure is likely to carry a relatively high risk in a fetus with poor cardiac function, compared to other indications.[7] When fetal blood is obtained, we routinely send the sample for chromosome analysis, although chromosomal abnormalities are unusual in this situation.[1] Repeat echocardiograms may be necessary to exclude an occult arrhythmia, particularly an intermittent tachycardia.[8] Some of the metabolic causes may be difficult to exclude prenatally and so postnatal metabolic investigations should be instigated in cases where no cause has been identified. In fetuses that die either pre- or postnatally it is essential that appropriate fresh unfixed tissue samples be obtained, so that these are available for metabolic investigation. This is particularly important because some cases of dilated cardiomyopathy may recur in subsequent pregnancies. At our centre, this has occurred in two families, so obtaining the appropriate samples is essential to provide parents with an explanation of the cause. Despite extensive investigation, however, about half of the cases remain unexplained.

Hypertrophic cardiomyopathy

Echocardiographic features

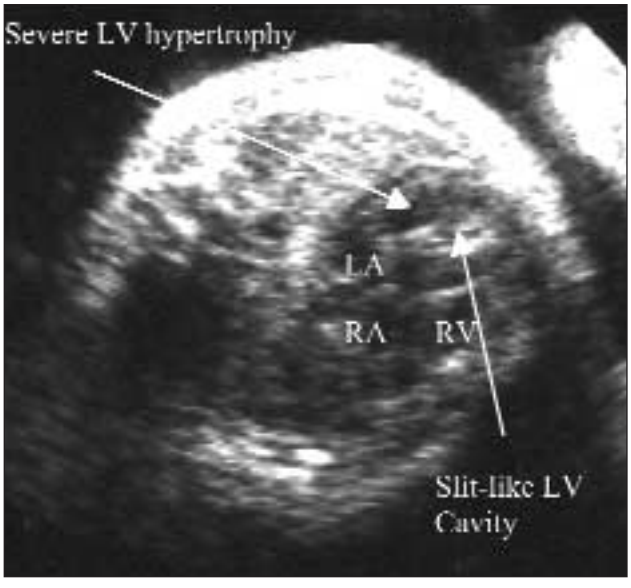
The unifying echocardiographic feature in this condition is severe ventricular hypertrophy that is not explained by any structural cardiac abnormality. Hypertrophy of the myocardium may affect either or both ventricles (Figures 24.7 and 24.8). Careful exclusion of obstructive lesions such as critical aortic stenosis or critical pulmonary stenosis is mandatory, to confirm that the hypertrophy is not secondary to outflow tract obstruction. This will involve Doppler interrogation of the left and right ventricular outflow tracts. In some fetuses, severe hypertrophy of the ventricle may lead to a dynamic obstruction of the outflow tract by the hypertrophied muscle (Figure 24.7b). Quantitation of the degree of ventricular hypertrophy may be helpful to follow disease progression. There are published normal ranges of septal and ventricular wall thickness using either cross-sectional[9] or M-mode echocardiography.[10]

Outcome

The outcome of hypertrophic cardiomyopathy will be influenced by the underlying cause. For example, diabetic cardiomyopathy generally resolves spontaneously following delivery. Overall, of 13 cases of hypertrophic cardiomyopathy identified at our centre between 1982 and 1995, there were four intrauterine deaths, three terminations of pregnancy, two neonatal deaths and four survivors.[11]

Causes

Myocardial hypertrophy may be the end result of a number of different disease processes. The causes that



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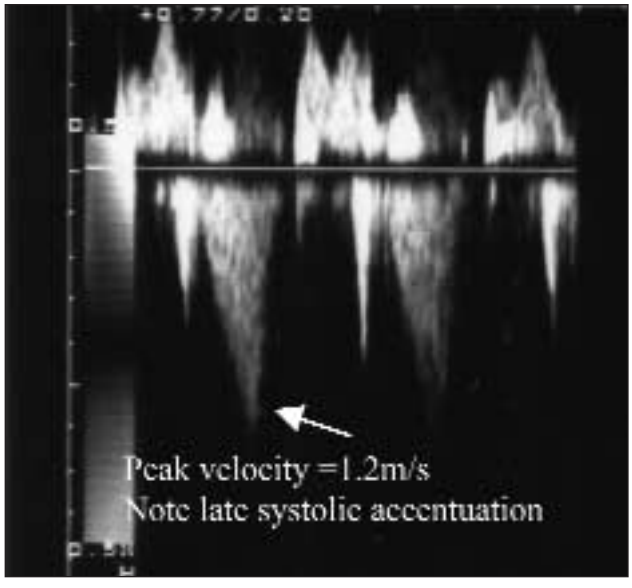

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Figure 24.7
(a) Hypertrophic cardiomyopathy in Noonan syndrome. There is marked hypertrophy of the left ventricle (LV) and ventricular septum. Views of the heart were limited, owing to advanced gestational age. The left ventricular cavity is slit-like. This fetus had increased nuchal translucency early in pregnancy and a normal karyotype. Hypertrophic cardiomyopathy developed late in gestation. Noonan syndrome was confirmed postnatally. RV, right ventricle; LA, left atrium; RA, right atrium. (b) Dynamic left ventricular outflow tract obstruction in the same fetus. The aortic Doppler is 1.2 m/s at 30 weeks' gestational age. Note the increased Doppler velocity in late systole confirming dynamic obstruction.

have been described in series in the literature are shown in Table 24.2. Some of the different groups of diseases that may lead to hypertrophic cardiomyopathy in utero are discussed below.

Table 24.2. Causes of hypertrophic cardiomyopathy

Maternal diabetes mellitus[6]
Genetic
Familial[12]
Noonan syndrome[1,6,11]
Chromosomal abnormality[15]
Metabolic
β-lipase deficiency[6]
Cytochrome oxidase deficiency[6,11]
Fetal renal disease[11]
Renal agenesis
Multicystic kidneys
Congenital nephrotic syndrome
Twin–twin transfusion syndrome

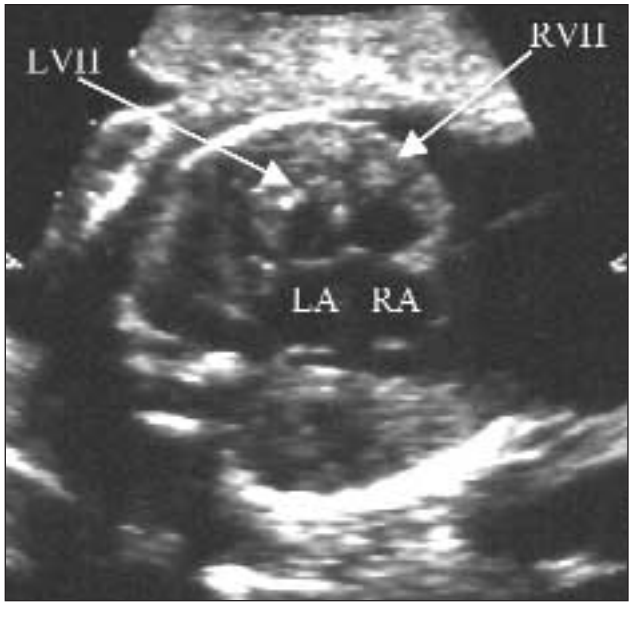

Figure 24.8
Hypertrophic cardiomyopathy. In this example there is a pericardial effusion. There is hypertrophy of both the left and right ventricles. No underlying cause was identified. LA, left atrium; RA, right atrium; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy.

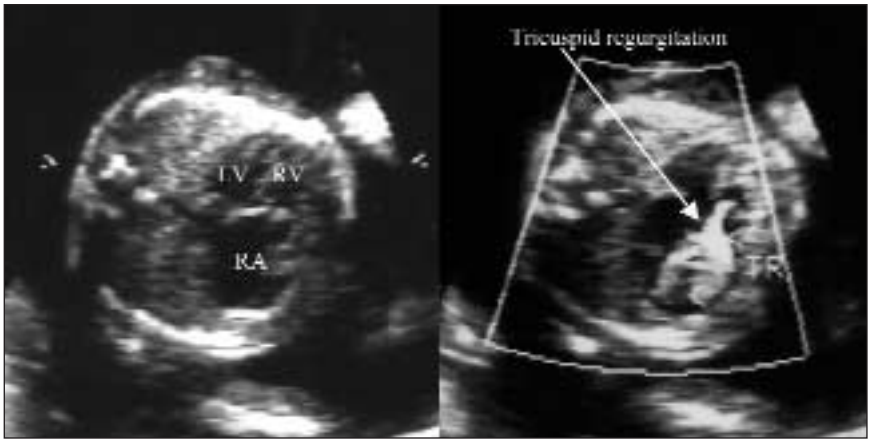

Figure 24.9
Appearances of the heart in twin-to-twin transfusion syndrome (recipient fetus). The right atrium (RA) is dilated secondary to marked tricuspid regurgitation. LV, left ventricle; RV, right ventricle.

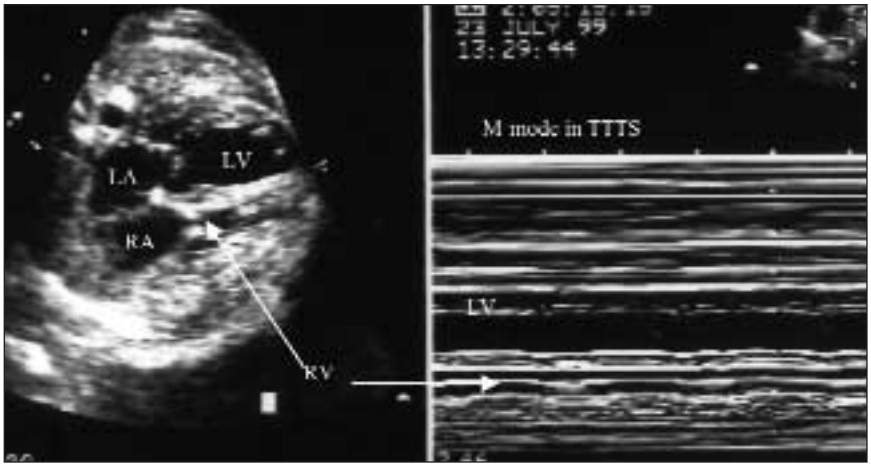

Figure 24.10
Twin-to-twin transfusion syndrome (recipient fetus). In this example the left ventricle (LV) is dilated with very poor systolic function on M-mode echocardiography. LA, left atrium; RA, right atrium; RV, right ventricle.

Diabetic hypertrophic cardiomyopathy

Maternal diabetes mellitus is an indication for detailed fetal echocardiography in view of the increased incidence of congenital heart defects in this group.[12] In addition, the most frequent cause of excessive ventricular hypertrophy in the fetus is maternal diabetes mellitus.[6] Such hypertrophy tends to occur late in pregnancy, typically beyond 30 weeks. Following delivery, ventricular hypertrophy resolves spontaneously, although in a minority of cases the infant may be symptomatic until the hypertrophy has resolved. Thus, if diabetic cardiomyopathy is to be detected prenatally, then echocardiography relatively late in pregnancy is indicated. Given that the myocardial hypertrophy resolves without therapy, and only a minority of newborn infants are symptomatic, the justification for sequential fetal echocardiography is debatable.

Genetic causes

Familial hypertrophic cardiomyopathy has been detected prenatally.[13] A normal fetal echocardiogram does not, however, exclude this diagnosis, because there may be progressive hypertrophy during childhood and adult life. Noonan syndrome has also been diagnosed postnatally in some fetuses presenting with hypertrophic cardiomyopathy during fetal life.[6,11,14] Some fetuses with Noonan syndrome will present initially with increased nuchal translucency and normal karyotype, which may be a useful clue to the underlying diagnosis.

Metabolic causes

Mitochondrial cytopathies may present with myocardial hypertrophy during fetal life although the total number of

reported cases is small.[6,11] Therefore, detailed metabolic investigations are indicated for unexplained ventricular hypertrophy, which may include endomyocardial biopsy.[16]

Renal disease

In the past, one of the main causes of unexplained ventricular hypertrophy in the fetus was renal disease in the fetus. The cause of the hypertrophy is difficult to establish with certainty, but fetal hypertension may be important. Such cases are increasingly identified by imaging of the renal tract, so that a diagnosis is usually made prior to fetal echocardiography.

Twin-to-twin transfusion syndrome

In twin-to-twin transfusion syndrome, a variety of effects have been observed on the heart of both the donor and recipient twin.[17,18] In the recipient twin, such effects include ventricular dysfunction, tricuspid regurgitation (Figures 24.9 and 24.10) and right ventricular outflow tract obstruction.[18] The cause of these findings is not entirely clear, but volume and pressure overload of the heart of the recipient fetus is a likely explanation of the functional abnormalities.[19,20] The reason why anatomic obstruction of the right ventricle occurs in some cases is not known.

Investigation of hypertrophic cardiomyopathy

The causes of hypertrophic cardiomyopathy in the fetus are diverse. In all cases a detailed fetal anomaly scan is mandatory to exclude associated malformations, particularly of the kidneys and renal tract. Exclusion of maternal diabetes mellitus is important because myocardial hypertrophy should resolve postnatally without treatment. Although unusual, chromosomal disease may manifest as hypertrophic cardiomyopathy prenatally,[15] thus fetal karyotyping should be considered. A normal fetal karyotype does not exclude underlying genetic disease such as Noonan syndrome. In cases where there is a family history of metabolic disease, prenatal genetic testing may be available, depending on the condition. When there is no family history, metabolic investigation may have to be deferred until postnatally, when appropriate samples may be obtained. If pregnancy results in intrauterine death or termination of pregnancy, some tissue samples should remain unfixed, so that metabolic analysis is still possible. Detailed postmortem examination should be discussed with parents to provide additional information on causation and recurrence risks. For both dilated and hypertrophic cardiomyopathies appropriate management is likely to involve a number of different subspecialists including a fetal cardiologist, fetal medicine specialist, clinical geneticist, specialist in metabolic disease and pathologists. Such a combined approach has the maximum chance of providing parents with an explanation of cardiomyopathy in their fetus or child.

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